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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1632	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/297,486	MARTIN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *10-13,16-36 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,14,15 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered as Paper No. 14 on 9/10/01. Applicant noted that the PTO form 326 accompanying the restriction requirement of Paper No. 13 indicated that only claims 1-36 were pending in the Application, whereas the actual restriction requirement acknowledged claims 1-38. Applicant requested clarification as to which claims are pending. Claims 1-38 are pending in the instant application.

Applicant's election with traverse in Paper No. 14 of group II claims 1-9, 14, 15, and 37, drawn to a method of treating or preventing intimal hyperplasia by administration of a nucleic acid encoding a VEGF receptor agonist is acknowledged. Traversal is on the grounds that no lack of unity was found during the PCT phase of the corresponding international application. This is unpersuasive because Applicant has failed to address the basis of the PTO's finding of a lack of unity, *i.e.* that the technical feature linking the claims was not a special technical feature under PCT Rule 13.2 because it was anticipated by the prior art. Applicant further argues that the use of a VEGF receptor agonist for the treatment or prevention of intimal hyperplasia relates to the same inventive concept as the use for this purpose of a nucleic acid encoding a VEGF receptor agonist. This argument is unpersuasive because it lacks support. These methods relate to a different inventive concept because they require different compositions comprising structurally and functionally distinct elements such as a VEGF agonist, and a nucleic acid encoding a VEGF agonist.

For these reasons the restriction requirement is still deemed proper and is made FINAL.

Nonetheless, the PTO notes several errors in the restriction requirement. First, there was a failure to identify any claims associated with Group V. Group V consisted of claims 14, 15, and 37, drawn to methods of therapy for a condition that can be treated or prevented by stimulation of NO or prostacyclin production, by administering a nucleic acid encoding nitric oxide synthase to a person or animal. Second, the nature of the inventions of groups I and II was incorrectly identified as methods of treating intimal hyperplasia by administration of a VEGF receptor agonist (group I) or a nucleic acid encoding a VEGF receptor agonist (group II). Groups I and II also embrace methods of therapy for a condition that can be treated or prevented by stimulation of NO or prostacyclin production by administration of a VEGF receptor agonist (group I) or a nucleic acid encoding a VEGF receptor agonist (group II). Finally the PTO failed to note that claims which are generic to more than one group will be examined only to the extent that they are defined by the elected group, although this was clear from the requirement itself. For example, claims 1-8 are generic to groups I and II, and claims 14, 15, and 37 are generic to groups I, II, IV, and V. Applicant's election of group II results in examination of claim embodiments limited to the scope of methods of therapy for a condition that can be treated or prevented by stimulation of NO or prostacyclin production by administration of a nucleic acid encoding a VEGF receptor agonist.

Claim Objections

Claims 1-9, 14, 15, and 37 are objected to because of the following informalities: Claims 1-9, 14, 15, and 37 are objected to because they recite non-elected subject matter. Specifically, these claims recite agents including agonists of a receptor to which VEGF binds. The elected subject matter includes only agents which encode agonists of a receptor to which VEGF binds.

Claims 14, 15, and 37 are objected to because they recite, "and/or" which is not a word. Deletion of "/or", and insertion of "one or both of" after "stimulation of" is suggested.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 14, 15, and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating intimal hyperplasia at a site of intimal thickening in a rabbit by administering to the site a DNA expression vector encoding an agonist of Flt-1 and Flk-1/KDR receptors, and for methods of stimulating angiogenesis and inducing re-endothelialization, as known in the prior art, does not reasonably provide enablement for treatment of any other vascular disorder in any species other than a rabbit, and does not reasonably provide enablement for treatment of any vascular disorder in any species using any

VEGF receptor agonist which is not an agonist for both Flt-1 and Flk-1/KDR receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As a preliminary matter, it is noted that the claims do not require any specific outcome as a result of the method steps (see rejection under 35 USC 112, second paragraph, below). As noted below under 35 USC 102 rejections, the prior art teaches methods of stimulating angiogenesis and re-endothelialization which employ the method steps of the instant invention. Because these methods were well known in the art at the time of filing, the specification is considered to be enabling for them.

The claimed invention embraces methods of treatment or prevention of intimal hyperplasia (claims 1-9), and methods of therapy for a condition that can be treated or prevented by stimulation of NO or prostacyclin production. The recited method steps require administration of a nucleic acid encoding any agonist of any receptor to which VEGF binds. There is no limitation on the site to which the nucleic acid is delivered, or the identity or function of the VEGF receptor (VEGFR). Only claim 8 limits the identity of the VEGFR agonist. Only claim 9 places any limitation on the mode by which the nucleic acid is delivered.

VEGF receptors and receptor agonists

The prior art teaches that there are at least three types of VEGF receptor: VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3. See Joukov et al (J. Biol. Chem 273(12): 6599-6602, 3/1998), page 6599, column 2, lines 1-20. While these receptors bind several agonists,

they do not all bind the same agonists. For example, VEGF binds both VEGFR-1 and VEGFR-2, while placental growth factor (PIGF) binds only VEGFR-1, and VEGF-C binds VEGFR-2 only. Furthermore, binding of these agonists results in different outcomes depending on the nature of the agonist and/or the location of the receptor. For example, Joukov et al teach that although both VEGF and VEGF-C bind VEGFR-2, VEGF promotes the growth of blood vessels, whereas VEGF-C promotes the growth of lymphatic vessels. See abstract, and page 6599, column 2, lines 15-19. Moreover, although PIGF is structurally similar to other members of the PDGF/VEGF family, and it binds to VEGF-1, its function *in vivo* was unknown at the time of filing. See Olofsson et al (Proc. Nat. Acad. Sci. USA 93: 2576-258, 3/1996) page 2576, last sentence of column 1. While the specification teaches that the function of the invention likely depends on binding VEGFR-1 and VEGFR-2 (see page 5, lines 14-19), no VEGFR agonist is excluded from the scope of claims 1-7, 9, 14, 15, and 37. However, the specification fails to teach how to use all VEGFR agonists in the invention, and in view of the fact that some VEGFR agonists have activities which are markedly different from VEGF, or are unknown, there is reason to doubt that these agonists could be used in the invention as claimed.

Nucleic acid-mediated therapy and in vivo vector targeting

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all

basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

Because the instant claims do not limit the mode of delivery of nucleic acids, the claims embrace systemic delivery of the therapeutic nucleic acid compositions. However, while progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller (1995) reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at

the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998) reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma (1997) clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal (1995) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). While the specification supports efficient transfer for direct application of nucleic acids to the site of intimal thickening in a rabbit, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector

targeting such that efficient gene transfer is achieved by any other mode of delivery. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

With specific respect to therapies based on the transfer of VEGF to the arterial wall, Laitinen (Pharm. Res. 47(4): 251-254, 4/1998) teaches that although promising effects on cardiovascular diseases have been noted by adventitial delivery of genes in animal models using the collar device disclosed at page 16, lines 21-23 of the specification, "further studies regarding gene transfer techniques, vectors, and safety of procedures are needed before a full therapeutic potential of gene therapy in vascular diseases can be evaluated." See abstract. See also sentence bridging pages 252 and 253, and last sentence of CONCLUSIONS on page 253. Thus the treatment of vascular diseases in general by delivery of VEGF nucleic acids was unpredictable at the time the invention was filed.

Hypertension and diseases related to NO and prostacyclin production

The claims explicitly encompass methods of treating hypertension, and in particular, essential hypertension, pulmonary hypertension, and cor pulmonale. Robbins (In Pathologic basis of Disease, 5th Edition, W.B. Saunders Company, Publishers, 1994) teaches that essential hypertension is caused by a primary increase in cardiac output due to reduced renal sodium excretion, or by vasoconstrictive influences including behavioral factors, increased release of

vasoconstrictors such as angiotensin II or catecholamines, or an increased sensitivity of vascular smooth leading to increased contraction. See page 485, column 1, first sentence of first full paragraph; page 487, column 1, line 5 to column 2, line 6. Although the specification teaches how to inhibit intimal proliferation in a rabbit model, intimal proliferation does not appear to be recognized in the art as a cause of essential hypertension. Furthermore the specification fails to teach how to use the instant invention to increase renal sodium excretion, affect behavioral factors responsible for hypertension, decrease the release of vasoconstrictors, or an decrease the sensitivity of vascular smooth leading to increased contraction. The specification indicates at page 6, lines 4-10 that NO levels are low in individuals suffering from hypertension, and concludes that VEGF may be useful in treating hypertension because it causes an increase in NO. However, no cause and effect relationship between NO levels and hypertension is established in the specification or the prior art of record. Thus it is no more likely that low NO levels cause hypertension than it is that low NO levels are caused by hypertension, thus there is insufficient evidence to indicate that increasing NO levels would reduce any type of hypertension. Even if increasing NO levels did decrease hypertension, the specification has failed to teach how much of any VEGFR agonist is required to produce sufficient NO for this effect, how to produce the appropriate amount of the agonist *in vivo,* or where to produce it. The specification also fails to identify a single disease which is related to prostacyclin production, fails to teach how much VEGF agonist should be expressed in order to stimulate prostacyclin production, how much prostacyclin production is required to treat any disease, where it should be produced, or how to

obtain the appropriate amount of VEGF expression. Moreover, Yla-Herttuala and Martin, co-inventors in the instant Application, indicated in a paper published 1/15/00 that the design of strategies in which VEGF genes are delivered for the purpose of stimulating therapeutic levels of NO and prostacyclins might be possible in the future. See page 217, paragraph bridging columns 1 and 2. In light of this statement, and the state of the art as established by Orkin, Verma, and Anderson above, one must conclude that the practice of stimulating therapeutic NO and prostacyclin production by VEGF nucleic acid administration was not routine and was highly unpredictable at the time of the invention. Yla-Herttuala and Martin also stress the need for further developments in gene-transfer vector and, gene delivery techniques before the therapeutic potential of gene therapy in cardiovascular disease can be assessed. See abstract. In view of the state of the art of gene therapy at the time of the invention, and after time of the invention as acknowledged by the inventors, and the failure of the specification to provide sufficient teaching or examples, one of skill in the art would have to perform undue experimentation to treat hypertension, or to stimulate therapeutic NO or prostacyclin production, using the methods of the instant invention.

Relevance of animal models of intimal hyperplasia to human disease and treatment

The prior art teaches that successful treatment of intimal hyperplasia in small animal models is not predictive of success in other animals, particularly in humans. Muller et al (J. Amer. Coll. Cardiol. 19(2):418-432, 1992) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in

response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid metabolism, and the activity of coagulation and fibrinolytic systems. The instant specification teaches a single example of a therapeutic result in a rabbit model of intimal hyperplasia by delivery of a liposomal composition comprising plasmid DNA encoding VEGF to the precise site of intimal thickening. See Example 1, pages 33-38. With respect to rabbit models, Muller notes that rabbit arteries are not necessarily structurally equivalent to human arteries. For example, the amount of elastin in the media of coronary arteries is less than that in larger mammals, the intima is thinner, and the subendothelial space between the endothelium and the internal elastic lamina is very narrow and virtually acellular. A similar intimal structure is found in the arteries of humans only during fetal and early neonatal life. See paragraph bridging columns 1 and 2 on page 420. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies. See abstract. Lafont et al (Ann. Card. Ang. 44(7): 349-353, 9/1995), review the results of fifteen years of research prior to 1995, and conclude that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from

experimental models which are very different from the atheromatous lesions observed in man". See abstract. Lafont et al (Card. Res. 39(1): 50-59, 7/1998) further indicates that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." See page 54, column 2, lines 3-12. The same concerns would apply to the treatment of hypertension and stenosis, due to the differences in physiology among the various models. In fact, the unpredictability in extrapolating results of such studies to humans was noted as late as 1999, when Johnson et al taught that small animal models "lacked efficacy in predicting the success of interventions to inhibit restenosis in humans", and found that small animal models fail to closely simulate human atherosclerosis and stenotic lesions. See abstract. For these reasons, even if the specification provided adequate guidance to one of skill in the art to practice the full scope of the invention in rabbits, which it does not, the enabled use of the claimed invention would be limited to the treatment of rabbits.

In summary, at the time of the invention, those of skill in the art recognized that one could not accurately extrapolate positive results from rat models of smooth muscle cell proliferation to other animals, particularly humans; the specification fails to improve on this situation by providing guidance which would allow such extrapolation; the specification fails to provide any working example of treatment in any organism other than a rabbit, or of any disorder

other than intimal hyperplasia; the specification fails to teach how to perform the claimed methods by delivering nucleic acids to any site other than a site of intimal thickening, or with any VEGFR agonist other than those which bind and agonize both Flt-1 and Flk-1/KDR receptors. For these reasons, one of skill in the art could not practice the claimed methods commensurate in scope with the claims without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 14, 15, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 14, 15, and 37 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claims recite no step in which treatment is effected. Also, it is unclear what constitutes an "effective amount of an agent" because the direct effect of administration of the agent is unknown. Because it is unclear what the agent must do in the method, it is unclear what is "an effective amount".

Claims 1-9 are indefinite because they recite "the endothelium" without proper antecedent basis. These claims are also indefinite because they recite the term "largely", which is a relative term. The term "largely" is not defined by the claim, the specification does not provide

a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, the amount of endothelium which must be intact, and the required degree of intactness, cannot be determined from the claim, thus the metes and bonds of the claim are unclear.

Claim 7 is indefinite because it recites "the function of human VEGF" without antecedent basis. Human VEGF can be construed as having several functions. For example, the function of VEGF could be construed as VEGF receptor binding, alternatively it could be construed as promoting angiogenesis. This is not a trivial distinction because, for example, VEGF-C also binds VEGF receptors, but it does not promote angiogenesis. See e.g. Joukov et al (J. Biol. Chem 273(12): 6599-6602, 3/1998), abstract, and first full paragraph of column 2 on page 6599. Thus the breadth of the genus of "proteins having the function of human VEGF" is unclear.

Claim 8 is indefinite because it is unclear what are the metes and bounds of "an active fragment" of the recited proteins. More specifically, it is unclear what constitutes activity. The fragment could act simply to bind to a receptor, alternatively the fragment could act to stimulate angiogenesis. As discussed above, different VEGF receptor agonists can exert different functions. Because the claim does not make clear what activity is required, it is unclear what would constitute "an active fragment".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-9, 14, 15 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by either of two US Patents issued to Isner (Nos. 6,121,246, or 6,258,787).

6,121,246 teaches a method of inducing formation of new blood vessels by injecting into a human host an effective amount of a DNA sequence encoding vascular endothelial growth factor. See claim 2 at column 13. The nucleic acid may be in a viral or liposomal vector. See column 5, lines 51-53. The DNA may also encode active fragments of VEGF such as VEGF-165. See column 6, lines 61-66 and column 7, lines 7-12. The instant specification teaches that VEGF-165 is equivalent to SEQ ID NO:4 of instant claim 8. Although 6,121,246 is silent as to treatment of the disorders recited in the instant claims, the claims of 6,121,246 recite the same method steps as the instant claims and can be considered to have the same results. It is noted that none of the instant claims recites any result associated with the method steps, for this reason an anticipation rejection is appropriate.

Thus 6,121,246 anticipates the claims.

6,258,787 teaches a method for inducing re-endothelialization in a blood vessel by administration of a nucleic acid encoding VEGF, wherein the blood vessel comprises a portion which is denuded of its epithelial lining. See claim 2 at column 19. The nucleic acid may be delivered in a liposomal or a viral vector. See column 6, lines 11-18. The nucleic acid may encode active fragments of VEGF such as VEGF-165. See column 9, lines 39-55. The instant specification teaches that VEGF-165 is equivalent to SEQ ID NO:4 of instant claim 8. The specification teaches that the blood vessel may be partially denuded of its endothelium by use of an arterial balloon catheter. See e.g. column 2, lines 20-27. Because denudation would only occur at the site of expansion of the balloon, the endothelium of the rest of the blood vessel should remain largely intact. Although 6,258,787 is silent as to treatment of the disorders recited in the instant claims, the claims of 6,258,787 recite the same method steps as the instant claims and can be considered to have the same results. It is noted that none of the instant claims recites any result associated with the method steps, for this reason an anticipation rejection is appropriate.

Thus 6,258,787 anticipates the claims.

Claims 1-9, 14, 15, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by either one of Isner et al (LANCET 348:370-374, 8/1996) or Takeshita et al (Biochem. Biophys. Res. Comm. 227:628-635 10/14/96).

Isner teaches a method of inducing formation of new blood vessels by injecting into a human host an effective amount of a DNA sequence encoding VEGF-165. The nucleic acid was delivered in a hydrogel polymer vector. See abstract and paragraph bridging columns 1 and 2 on page 370. The instant specification teaches that VEGF-165 is equivalent to SEQ ID NO:4 of instant claim 8. Although Isner is silent as to treatment of the disorders recited in the instant claims, Isner recites the same method steps as the instant claims and can be considered to have the same results. It is noted that none of the instant claims recites any result associated with the method steps, for this reason an anticipation rejection is appropriate.

Thus Isner anticipates the claims.

Takeshita teaches a method of inducing formation of new blood vessels by injecting into a human host an effective amount of a DNA sequence encoding VEGF-165. The nucleic acid was delivered in a hydrogel polymer vector. See abstract, and page 629, lines 4-7 of second paragraph. The instant specification teaches that VEGF-165 is equivalent to SEQ ID NO:4 of instant claim 8. Although Isner is silent as to treatment of the disorders recited in the instant claims, Isner recites the same method steps as the instant claims and can be considered to have the same results. It is noted that none of the instant claims recites any result associated with the method steps, for this reason an anticipation rejection is appropriate.

Thus Takeshita anticipates the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

Richard Schnizer, Ph.D.